Tramadol Use in Zoologic Medicine

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- Tramadol
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THE NEED FOR ANALGESIA IN ZOOLOGIC SPECIES

Analgesia is becoming increasingly important in veterinary medicine, and controlling pain in zoologic animals is an important component to improving the welfare of captive animals. Behaviors associated with pain are variable between species, and some animals may not show signs until severely distressed. Careful observation of behavior by animal care staff can aid in the recognition and therefore treatment of painful conditions in zoologic animals.

Numerous analgesics are available for use in animals, but a few have been extensively used or studied in zoologic species. Tramadol is a new analgesic that is available in an inexpensive oral form and is not controlled. Tramadol may be an alternative to other analgesics, such as opioids and nonsteroidal antiinflammatory drugs, when treating acute or chronic pain in zoologic animals.

MECHANISM OF ACTION OF TRAMADOL

Tramadol is a centrally acting analgesic drug that is licensed and used in humans.[1] Its analgesic efficacy is a result of complex interactions between the opiate, adrenergic, and serotonin receptor systems.[1] It is both a weak opioid agonist with selectivity for the μ-receptor (opioid μ receptor) and a weak inhibitor of the reuptake of norepinephrine and serotonin (5-hydroxytryptamine). This dual mechanism of action may be attributed to the 2 enantiomers of racemic tramadol. The 2 enantiomers act synergistically to provide analgesia. The S(+) enantiomer of tramadol has a low affinity for μ-receptors. This enantiomer inhibits the cellular reuptake of serotonin and increases its extracellular release. The R(−) enantiomer more effectively inhibits norepinephrine reuptake and increases its cellular release by autoreceptor activation.[1,2] Tramadol provides analgesia mainly via the serotonin and norepinephrine pathways.

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Hepatic demethylation of tramadol produces the active metabolite *O*-desmethyltramadol (M1), which also exists as a racemic mixture. The S(+)-M1 interacts with μ-receptors, whereas R(−)-M1 interacts with α_2-adrenergic receptors.[3] The S(+)-M1 is reported to be 2 to 200 times more potent in μ-receptor binding as S(+)-tramadol.[4,5] A large portion of the analgesic effect of tramadol is because of the M1 metabolite[6–8]; thus, a variability in the biotransformation of tramadol into M1 might clearly affect the analgesic effect and treatment response.

The demethylation reaction to produce M1 in humans is metabolized by the cytochrome P450 (CYP) 2D6 isoenzyme (CYP2D6).[9,10] CYP2B6 and CYP3A4 are also primarily involved in the formation of metabolites, M5 and M3, respectively.[11,12] The wide variability in the pharmacokinetic properties of tramadol in human beings can partly be attributed to CYP genetic polymorphism.[9] The existence of different alleles in humans results in functionally different enzymes.[13] Studies in humans also indicate that biphasic kinetics occur for the formation of the metabolites M1 and M2, which indicates the participation of more than one CYP isoform in the tramadol metabolism pathway.[13] Because of the large degree of variation in metabolism, pharmacokinetic parameters must be established for each species. The pharmacokinetics of tramadol and its metabolites have been reported in humans,[1,13] dogs,[14–18] cats,[19–21] horses,[22–26] goats,[27] donkeys,[28] llamas,[29] and camels.[30] Several studies indicate interspecies differences in drug metabolism.

Opioid peptides of the mammalian central nervous system are grouped into 3 families: the enkephalin, the dynorphin, and the endorphin peptides. These peptide families exert their effects on the nervous system by interacting with 3 specific endogenous opiate receptors.[31] Opioid peptides have been found in the nervous system of all classes of vertebrates, including amphibians, reptiles, and birds, and many different invertebrate groups.[31] Opioid drugs mediate their effects by binding to G protein–coupled receptors that are also activated by endogenously produced opioid neuropeptides. The 3 pharmacologically distinct types of mammalian opioid receptors μ, δ, and κ are encoded by separate structural genes.[32] μ-Receptors are of primary importance for mediating the effects of opioid drugs in mammals and play a role in other vertebrates as well. These receptors are present in the brains of birds,[31] reptiles,[33] amphibians,[34] and fish.[35] The distribution of μ-receptors depends on the species as well as on the region of the brain examined. Opioid κ and δ receptors (κ- and δ-receptors, respectively) are also present across species, and studies in birds have suggested that κ-receptors may be more important than μ-receptors in producing analgesia.[36]

Tramadol has a wide margin of safety in humans, with minimal respiratory, cardiovascular, or gastrointestinal side effects.[1,13,37] Opioid analgesics are generally associated with respiratory depression, which is mediated through a decrease in the sensitivity of the respiratory center to carbon dioxide that results in a decrease in the respiratory rate. Studies in humans indicate that unlike other opioids, tramadol is not likely to produce clinically significant respiratory depression.[1] Tramadol has no clinically relevant effects on blood pressure or heart rate. In healthy human patients, heart rate and blood pressure were only slightly elevated after intravenous (IV) administration of tramadol.[13] In contrast to other μ-receptor agonists, tramadol has only minor effects on gastric emptying. In a long-term study, tramadol was found to have only a minor delay on colonic transit time but no effect on upper gastrointestinal tract transit or gut smooth muscle tone.[13]

Tramadol and M1 also inhibit the reuptake of norepinephrine (noradrenaline) and serotonin, which are important activating components of the descending pain inhibitory system.[37–39] When the descending pain inhibitory system is activated, the transmission of painful stimuli through the dorsal horn of the spinal cord is inhibited by the action of endogenous opioids.[39] By inhibiting the reuptake of both norepinephrine and serotonin, tramadol activates the descending pain inhibitory system, therefore decreasing the sensation of pain. These 2 mechanisms of action of tramadol, binding to opioid receptors and activation of the descending pain inhibitory system, work synergistically to provide analgesia in vertebrate species. One study also suggested that tramadol may provide analgesia by antagonizing *N*-methyl-D-aspartate (NMDA) receptors.[40] NMDA receptors are located throughout the nervous system, as well as in the viscera. Antagonism of NMDA receptors reduces the hyperexcitability of nociceptive neurons in the dorsal horn of the spinal cord, therefore decreasing pain.[41,42] Other metabolites, including M2, M3, M4, and M5, have been described, but it is unknown whether they have analgesic properties.[7]

Tramadol can interact with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors, so tramadol should be used with caution in patients on these medications.[1] Also, concomitant administration of carbamazepine, cimetidine, and quinidine results in their interaction with tramadol, and hence, they should be used cautiously.[1] Patients with opiate sensitivity could experience dysphoria, agitation, and sedation as possible side effects to administration of tramadol.

At present, only oral preparations of tramadol are available in the United States; however, injectable preparations are available in Europe and South America. Unlike morphine and other opioids, tramadol is not a scheduled drug controlled by the Drug Enforcement Agency, a component of the US Department of Justice.

TRAMADOL USE IN HUMANS AND DOMESTIC ANIMALS

Humans

Tramadol is rapidly absorbed after a single or multiple oral doses of 100 mg in adult volunteers.[1] The elimination half-life after a single oral (100 mg) or parenteral (50 mg) dose in adults was 5.5 hours, whereas the half-life of M1 after oral doses was 6.69 hours.[1] Grond and Sablotzki[13] reviewed multiple human studies and found that the half-life of tramadol ranged from 5 to 6 hours. Tramadol half-life is roughly increased by 2-fold in patients with renal or hepatic impairment. M1 is the primary metabolite formed in humans; however, there are interindividual differences in metabolism, which may be due to the genetic polymorphism of CYP2D6.[43] The most common side effects in humans are nausea, dizziness, drowsiness, tiredness, sweating, and vomiting.

The analgesic efficacy of IV, intramuscular (IM) and oral tramadol has been established in extensive studies in adult patients with moderate to severe acute postoperative pain.[1,13] Tramadol has also been used in the treatment of posttraumatic, obstetric, and renal pain. Parenteral or oral tramadol was effective in relieving moderate to severe postoperative pain associated with several types of surgery, by reducing pain intensity by 47% to 58% within 4 to 6 hours.[1] The overall analgesic efficacy of tramadol is comparable to that achieved using equianalgesic doses of parenteral morphine or alfentanil.

In humans, the reported minimally effective analgesic plasma concentrations range from 298 ± 171 ng/mL to 590 ± 410 ng/mL for tramadol and 39.6 ± 29.5 ng/mL to 84 ± 34 ng/mL for M1.[44,45] It has been suggested that in humans, the clinically effective target plasma concentration of tramadol to treat mild to moderate pain can be as low as 100 ng/mL.[46]

Dogs

The use of tramadol in dogs has been investigated in several studies.[14–18] The pharmacokinetics of tramadol and its active metabolite M1 was determined after IV and oral administration of tramadol at 4.4 mg/kg and 100 mg, respectively, to 6 adult beagles.[14]

No adverse effects were noted after either dose; however, dogs administered with 1 mg/kg of M1 exhibited signs of nausea, including salivation and increased swallowing. After IV and oral administration, the half-life of tramadol was 1.80 and 1.71 hours, whereas the half-life of M1 was 1.69 and 2.18 hours, respectively. The maximum concentration (C_{max}) for tramadol after oral administration was 1402.75 ng/mL, whereas that of M1 after IV and oral administration was 146.90 and 449.13 ng/mL, respectively. Kukanich and Papich[14] suggest that the short elimination half-life of M1 after oral tramadol administration to dogs would require frequent dosing to maintain target plasma concentrations but steady state would be reached rapidly. They also suggest that M1 is a minor metabolite in dogs when compared with other metabolites not measured. Based on the information from their study a simulated oral dosing regimen of 5 mg/kg every 6 hours or 2.5 mg/kg every 4 hours is predicted to produce tramadol and M1 concentrations that are consistent with producing analgesia in humans. McMillan and colleagues[15] also found that M1 was present but at very low levels after 1, 2, and 4 mg/kg of IV administration to 6 male mixed breed dogs. The low levels of M1 detected and the close proximity to the lower limit of quantification, which was between 9.8 and 1937 ng/mL, did not permit the evaluation of pharmacokinetic parameters. One dog in the study developed nausea and increased salivation after each dose, and sedation scores increased with increasing doses in all dogs. There were no effects on heart or respiratory rates after any of the doses. McMillan and colleagues[15] also suggest that the rapid elimination rate has implications when designing dosage regimens in dogs and may result in failure of analgesia if canine dosage regimens are based on human studies. Dogs require more frequent doses to maintain adequate therapeutic drug concentrations.

Vettorato and colleagues[16] found that M1 was a prominent metabolite after IV administration of 2 mg/kg of tramadol to dogs for surgery. Variable concentrations of both tramadol (5.00–0.09 μg/mL) and M1 (0.35–0.09 μg/mL) were noted in the study. Breeds, gender, body weight, and ages were not standardized, and it is suggested that these factors might have influenced the variable M1 formation rate. Tramadol was administered extradurally to dogs undergoing tibial plateau leveling osteotomy and found to produce adequate intra- and postoperative analgesia without significant side effects. However, the analgesia produced was not superior to that obtained after IV administration; therefore, the extradural route was considered an impractical alternative to IV tramadol administration in dogs.

Giorgi and colleagues[17,18] examined the profile of tramadol in dogs in 2 different studies. In the first study, 100 mg of tramadol was given IV, IM, orally (immediate and sustained release capsules), and rectally to 6 male beagles.[17] After IV and IM injections, animals exhibited some side effects such as excitation and tremors but these effects were transient and resolved within 1 hour. In the second study, 4 mg/kg of tramadol was administered via suppositories and IV injection to 6 male beagles.[18] There were no adverse effects after either dose. The half-life for tramadol was 1.02 and 2.24 hours after IV and rectal administration, respectively, whereas the C_{max} after rectal administration was 134 ng/mL. M1 was detected in negligible amounts near the limit of quantification, which was 5 ng/mL.

Based on a descriptive and visual analog scale, Mastronique and Fantoni[47] found that in 30 female dogs of different breeds and ages undergoing ovariohysterectomy, the analgesic effects of IV tramadol (2.0 mg/kg) were equivalent to those produced by IV morphine (0.2 mg/kg). In a recent study on electroencephalographic responses to acute noxious electric stimulation responses, tramadol, parecoxib, and morphine were compared in anaesthetized dogs.[48] The study found that morphine (0.5 mg/kg subcutaneously) prevented any increase in F50 (median frequency) after noxious electric stimulation, whereas both tramadol (3.0 mg/kg subcutaneously) and parecoxib failed to prevent an increase in F50 because of uninhibited nociceptive transmission to the cerebral cortex in response to the same stimuli.

Seddighi and colleagues[49] studied the effects of tramadol on the minimum alveolar concentration (MAC) of sevoflurane in dogs. They found that tramadol significantly reduced the MAC, but it was not dose dependent at the doses studied, which ranged from 1.5 to 3.0 mg/kg.

Cats

Pypendop and Ilkiw[19] administered 2 mg/kg IV and 5 mg/kg oral tramadol to 6 adult female cats. No adverse effect was observed after either dose; in fact, the cats appeared euphoric for several hours. After IV and oral administration, the half-life of tramadol was 2.23 and 3.40 hours, whereas the half-life of M1 was 4.35 and 4.82 hours, respectively. The C_{max} for tramadol was 1323 and 914 ng/mL, whereas that of M1 was 366 and 655 ng/mL after IV and oral administration, respectively. This result is similar to the results obtained in another study in which tramadol was administered at 2 mg/kg IV and had a half-life of 2.18 hours.[20] Pypendop and Ilkiw[19] suggest M1 is one of the main metabolites produced in cats. Pypendop and colleagues[21] continued their work in cats with a study on the pharmacodynamic effects of tramadol. Oral doses of 0.5, 1.0, 2.0, and 4.0 mg/kg tramadol in gelatin capsules were used, which produced mean plasma tramadol levels from 25.8 to 539.8 ng/mL and mean M1 levels from 94.5 to 480.4 ng/mL. They found that tramadol did induce thermal antinociception in cats; however, doses of 2 mg/kg or more were necessary to yield a significant and sustained effect. This result agrees with results from another study in which tramadol administered at 1 mg/kg subcutaneously had minimal or no effect on thermal and mechanical thresholds in cats.[50] Some of the behavioral and physical effects, such as euphoria and mydriasis, observed after administration of tramadol were similar to the classic effects observed after administration of moderate doses of opioids in cats. No clinically important adverse effects were observed in the cats for any of the doses. Data from the study suggested that to achieve 95% of the maximum thermal antinociceptive effect of tramadol, plasma concentrations of approximately 350 ng/mL would have been required. This concentration would be within the range of higher concentrations that provide postoperative analgesia in humans. Simulation based on pharmacokinetic parameters for tramadol in cats reported in another study and pharmacodyanmics of this study by Pypendop and Ilkiw[19] predict that administration of 4 mg/kg tramadol every 6 hours results in plasma tramadol concentrations of 350 ng/mL or more for 89% of the time overall and more than 90% of the time after the last 3 doses.

Ko and colleagues[51] studied the effects of tramadol on the MAC of sevoflurane in cats. Results indicated that oral administration of tramadol reduced MAC of sevoflurane and that the magnitude of this effect was an intermediate between that of butorphanol and hydromorphone. This reduction was thought to be because of tramadol's effects on opioid receptors and was reversible with the administration of naloxone. Analgesic effects of tramadol were also compared with those of morphine after their epidural administration in cats, and tramadol was found to provide analgesia for the first 6 hours after administration.[52]

Goats

DeSousa and colleagues[27] examined the pharmacokinetics of tramadol after an oral and IV administration of 2 mg/kg tramadol to 6 female goats. No adverse effects were noted after either dose. The half-life for tramadol was 0.94 and 2.67 hours after IV and oral administration, respectively. Tramadol levels were measurable for 3 and

2 hours after oral and IV administration, respectively, with a C_{max} of 542.9 ng/mL after the oral dose and an initial concentration (C_0) of 3200.0 ng/mL after the IV dose.

M1 was in detectable levels after IV administration and had a half-life of 2.89 hours but was not detectable in the plasma after the oral dose. Based on information from the study it was suggested that an IV dose of 4 mg/kg given every 6 hours should produce tramadol and M1 concentrations consistent with analgesia in humans. To date, no pharmacodynamic studies have been done with tramadol in goats to evaluate the analgesic efficacy.

Camels

One study has determined the pharmacokinetics of tramadol in camels. Elghazali and colleagues[30] administered 2.33 mg/kg of tramadol via IV and IM injections to 6 (3 male, 3 female) healthy camels. No adverse effects were observed after either dose. The half-life of tramadol was 1.3 and 3.2 hours after IV and IM administration, respectively. The C_{max} and C_0 of tramadol were 0.44 and 1.40 μg/mL after IV and IM dosing, respectively. M1 was detected in urine but was not quantified. As yet, no pharmacodynamic studies have been done with tramadol in this species to evaluate the analgesic effectiveness.

Llamas

In a study, 6 adult male llamas were administered 2 mg/kg tramadol either IV or IM[29] Adverse effects were observed during the IV administration in the last llama, which had muscle twitching and ataxia. This effect lasted for roughly 15 minutes, after which no further adverse effects were observed; however, no adverse effects were noted after IM administration. The half-life for tramadol was 2.12 and 2.54 hours, whereas the half-life for M1 was 10.40 and 7.73 hours after IV and IM administration, respectively. After IV and IM administration, tramadol concentrations ranged from 4036 to 9 ng/mL and 1360 to 9 ng/mL, whereas M1 concentrations ranged from 158 to 39 ng/mL and 158 to 29 ng/mL, respectively. Based on information from the study, a simulated oral dosing regimen of 4 mg/kg of tramadol given IM every 12 hours is predicted to lead to plasma concentrations in the average animal, which are associated with analgesia in humans. To date, no pharmacodynamic studies have been conducted with tramadol in this species to evaluate the analgesic effectiveness.

Donkeys

In a study conducted by Giorgi and colleagues,[28] 12 male donkeys received a dose of 2.5 mg/kg tramadol either IV or orally (immediate release capsule). Tramadol half-life was 1.5 and 4.2 hours after IV and oral administration, respectively, and no adverse effects were observed with either dose. The C_{max} for tramadol after oral administration was 2817 ng/mL. After IV administration, M1 concentrations were higher than the minimum effective plasma concentration of 80 ± 60 ng/mL reported in humans, for a period of 5 minutes to 8 hours, which suggested a long-acting effectiveness of the drug. There was a limited production of M1 after oral administration, which may result in decreased analgesic efficacy when this route is used. To date, no pharmacodynamic studies have been performed with tramadol in this species to evaluate the analgesic effectiveness. Clinical effectiveness of tramadol has been questioned in species that mainly metabolize it to inactive metabolites, suggesting that this drug may not be an effective and safe analgesic in humans.

Horses

There are several studies involving the use of tramadol in horses.[22–26] Tramadol was administered IV to 5 horses (male and female) at a dose of 2.5 mg/kg in a study conducted by Zonca and colleagues.[25] No adverse effects were observed in the treated animals. The half-life of tramadol was 1.29 hours, and although M1 was present in quantifiable concentrations in all samples, no further information was provided. These results are similar to those seen in another study in which 5 horses were administered tramadol, 2 mg/kg IV, and the half-life was 1.36 hours.[22] However, adverse effects were observed during IV administration in the first 2 animals, which had muscle twitching that lasted 10 to 15 minutes. These effects occurred when tramadol was administered over 5 to 6 minutes. When tramadol administration was prolonged to 10 minutes, the adverse effects were not observed. Shilo and colleagues[22] administered tramadol IM and orally to 7 horses, and the half-life and C_{max} of tramadol were 1.53 hours and 637 ng/mL, respectively, after IM administration; however, absorption was poor after oral administration, with only 3% found in systemic circulation, and therefore half-life was not calculated. The C_{max} of tramadol after the oral dose was 33 ng/mL. Very low levels of M1 were also detected after IV, IM and oral administration.[22] Similar adverse effects were observed in a study in which horses were administered tramadol (2 mg/kg) IV, and hence, this portion of the study was discontinued.[26] However, tramadol was administered orally (2 mg/kg) to the same horses, with no adverse effects. The half-life for tramadol and M1 was 10.10 and 4.00 hours, respectively. The concentrations in this study ranged from 256 to 15 ng/mL and 47 to 11 ng/mL for tramadol and M1, respectively.

Giorgi and colleagues[23] administered tramadol, 5 mg/kg, IV to horses, and similar to other studies, the animals exhibited adverse effects, such as nausea, confusion, agitation, tremors, and tachycardia, in varying degrees. The effects started within 3 to 5 minutes of administration and resolved 2 hours after dosing. The plasma concentrations of M1 in this study[23] were only marginal, in agreement with the results of Shilo and colleagues.[22]

Dhanjal and colleagues[24] conducted a study on both the pharmacokinetics and pharmacodynamics of tramadol, 2 mg/kg, after its administration to 7 horses. Some side effects were evident, such as head nodding, sensitivity to noise, excitation, increased alertness, and trembling, which occurred in 5 of the 6 horses. The half-life and C_{max} for tramadol after IV administration were 2.05 hours and 2.2 μg/mL, respectively, and M1 concentrations were not quantified in the study. Tramadol, however, did not produce analgesia in the horses as determined by their response to a thermal nociceptive stimulus.

TRAMADOL USE IN ZOOLOGIC SPECIES

A few studies examining tramadol in zoologic species have been published; some are reviewed in the following sections. Research is available for several species regarding the efficacy of opioids, particularly morphine and other μ opioids; however, literature concerning the role of norepinephrine and serotonin in the analgesia of zoologic species is scant. Because of the lack of published studies or clinical trials using tramadol, dosing in zoologic species must often be estimated based on clinician experience or extrapolation from pharmacokinetic and pharmacodynamic studies in other species. Studies performed in domestic animals, as reviewed previously, can be tremendously helpful when choosing a dose of tramadol for a particular zoologic species. In addition, plasma concentrations of tramadol and M1 associated with analgesia have not been reported for zoologic species, with the exception of recent studies in parrots.[53]

Delivering medication to zoologic animals can be a challenge. Tramadol is commercially available as 50-mg tablets that can be hidden in food items that are eaten whole, such as meatballs, small rodents, and fish. Some animals may be unwilling to take the medication in a pill form, and a compounded suspension of tramadol has been evaluated for stability.[54] Wagner and colleagues[54] mixed crushed tramadol tablets with 1 of the 2 commercial suspension agents and found that both the solutions maintained approximately 99% of the initial drug concentration after 90 days at room temperature. Flavors can also be added to these suspensions to make them more palatable for various species.

Fish and Amphibians

One study found that analgesia was achieved when carps (*Cyprinus carpio*) were administered tramadol before an electric thermal stimulus.[55] Analgesia was dose dependent, lasted for 2 hours, and did not affect swimming or normal behaviors when compared with controls. Other studies have provided evidence that fish have similar nociceptive processing systems and opioid receptors as terrestrial mammals.[35,56,57] Studies are needed to determine the metabolism and analgesic efficacy of tramadol in various fish species.

Studies have been conducted to examine the opioid affinity and function of μ-receptors in frogs.[34] One study found that slight and profound analgesia was obtained after giving low-dose (10 mg/kg) and high-dose (100 mg/kg) morphine, respectively, in frogs (*Rana pipiens pipiens*) with no noticeable behavioral effects.[58] No reports of tramadol use in clinical cases or research in amphibians have been published, but μ-receptors are present and may play a role in analgesia.

Reptiles

Greenacre and colleagues[59] examined the analgesic effect of tramadol in bearded dragons (*Pogona vitticeps*) after a noxious electric stimulus. There was significant analgesia after oral administration of tramadol, 11 mg/kg. Another study showed that high-dose morphine (10 and 20 mg/kg) had analgesic effects in bearded dragons after a noxious thermal stimulus.[60] These studies suggest that μ-receptors may be primarily responsible in opioid-induced analgesia in bearded dragons. Further studies are needed to examine tramadol in other species of lizards to determine appropriate dosing regimens.

Research in turtles has suggested that opioid-mediated analgesia is primarily associated with μ-receptor activation, with a small contribution from δ-receptor activation.[61] Respiratory depression after μ- and δ-receptor activation has been reported in turtles.[62] A recent study found that when red-eared sliders were orally dosed with tramadol at 10 mg/kg, they had a delayed withdrawal from a noxious thermal stimulus when compared with controls.[63] This analgesic effect was present for 6 to 96 hours after dosing. Similar effects were observed with subcutaneous dosing but for a shorter duration postdosing (12–48 hours). The investigators concluded that when red-eared sliders were dosed orally with tramadol at 10 mg/kg, long-lasting effective analgesia was achieved.

No studies examining tramadol in snakes have been published. Response to opioids seems to be variable between species of snakes. One study examined physiologic responses (plasma cortisol and catecholamine levels, blood pressure, heart rate) of ball pythons (*Python regius*) after surgery and found no difference in control animals versus animals dosed with either meloxicam (0.3 mg/kg) or butorphanol (5.0 mg/kg).[64] The investigators concluded that at the doses administered, neither meloxicam nor butorphanol seemed to provide postoperative analgesia to ball pythons. Another study found that high doses of butorphanol (20 mg/kg), but not morphine, induced analgesia after a noxious thermal stimulus in corn snakes (*Elaphe* *guttata*).[60] Species-specific research may be required with snakes to determine the role of various opioid receptors and the analgesia-associated doses of tramadol.

A few studies addressing analgesia have been performed in crocodilians. One study evaluated the efficacy of morphine in crocodiles (*Crocodylus niloticus africana*) after a noxious thermal stimulus.[65] Morphine was injected intraperitoneally and doses of 0.5 to 1.0 mg/kg were found to provide antinociceptive effects. No research examining tramadol use in crocodilians is available.

Birds

Numerous studies have examined analgesics in several avian species. A pharmacodynamic study in African gray parrots (*Psittacus erithacus*) found that κ-agonists, such as butorphanol, were more effective analgesics than μ-agonists, such as buprenorphine.[36] One study in chickens found that administration of both μ- and κ-agonists led to a reduction of isoflurane minimum anesthetic concentration.[66] Fentanyl, a μ-agonist, administered to white cockatoos (*Cacatua alba*) produced analgesia, but some birds became hyperactive after administration.[67] A review of published avian analgesic studies shows a wide range of responses to administration of μ- and κ-opioids, indicating that both μ- and κ-receptors may play a role in opioid-mediated analgesia.

Tramadol has been examined in several avian species including bald eagles (*Haliaetus leucocephalus*),[68] red-tailed hawks (*Buteo jamaicensis*),[7,69] peafowl (*Pavo cristatus*),[70] and Hispaniolan Amazon parrots (*Amazon ventralis*).[53] Pharmacokinetic parameters varied between species.

The studies in bald eagles and red-tailed hawks did not involve the evaluation of tramadol's analgesic efficacy; the objective in both studies was to report the pharmacokinetics of a single dose of tramadol.[68,69] Recommended doses for raptors ranged from 5 mg/kg twice a day (bald eagles) to 8 mg/kg twice a day (red-tailed hawks). These doses were based on plasma concentrations of tramadol in eagles and hawks, which were in the same range as analgesic concentrations in humans. Clinically, with the above-mentioned dosages raptors become sedated after numerous doses; therefore, less-frequent administration or lower doses may be required for repeat dosing. Further studies in raptors examining pharmacodynamics, as well as the pharmacokinetics of repeat dosing, are needed.

Six peafowl were administered oral tramadol, and blood was collected over time.[70] Initial findings indicated that less-frequent dosing, possibly only once daily, would likely be needed to maintain plasma concentrations that are associated with analgesia in humans. Similar to raptors, further studies would be beneficial to examine species differences in metabolism and efficacy of the drug.

The pharmacodynamics and pharmacokinetics of tramadol are currently being evaluated in Hispaniolan Amazon parrots.[53] Initial data suggest that oral doses of 30 mg/kg are required to provide analgesia in response to a noxious thermal stimulus. This dose of tramadol provided significant analgesia for 6 hours after dosing when compared with controls. This higher dose may be necessary because of differences in absorption and metabolism when compared with other birds. Additional studies examining tramadol in Amazon parrots are being conducted at present. The initial findings in Amazon parrots reemphasize the importance of species-specific pharmacokinetic and pharmacodynamic research not only for birds but also for zoologic species in general.

Mammals

Tramadol use in various mammalian zoologic species has been reported,[71–73] but research has only been performed in a few species, predominately rodents and rabbits. Dosing is typically extrapolated from published studies in other closely related mammalian species.

A few studies have been performed in rodents, primarily in a laboratory animal medicine setting. One study found that intraperitoneally administered tramadol (10 mg/kg) abolished postoperative hyperalgesia in rats when compared with saline or parecoxib.[74] Another study in a rat experimental model suggested that oral tramadol doses as low as 0.45 mg/kg may provide analgesia; the researchers also found that tramadol can provide localized analgesia when administered subcutaneously at the site that would receive a noxious stimulus.[75] The same study suggested that tramadol and gabapentin may work synergistically to provide analgesia for rats. Rats administered with varying doses of intraperitoneal tramadol (1–25 mg/kg) showed delayed responses after thermal or ischemic noxious stimuli but they may have decreased motor function at higher doses.[76] In a clinical setting, tramadol is most commonly administered orally, and unfortunately, currently available research has not used this route of administration. Rodent studies examining the analgesic pharmacodynamics of tramadol at various oral doses are needed.

Rabbits were administered oral tramadol at 11 mg/kg, and blood samples were collected at various time points up to 6 hours postdosing.[77] Although the plasma tramadol and M1 concentrations associated with analgesia in rabbits are not known, these concentrations were less than those associated with analgesia in humans. The investigators concluded that administering oral tramadol at 11 mg/kg is unlikely to provide analgesia to rabbits for a clinically acceptable length of time. The low plasma tramadol concentrations in rabbits are similar to those found after oral dosing in horses. Another study evaluated the effect of tramadol on MAC of isoflurane (ISOMAC) in rabbits.[78] After IV administration of tramadol (4.4 mg/kg), there was a significant reduction of ISOMAC, but this reduction was thought to be clinically unimportant. Plasma tramadol and M1 concentrations at the time of ISOMAC reduction ranged from 181 to 636 ng/mL and 32 to 61 ng/mL, respectively. Until further research is conducted to determine appropriate oral doses, tramadol should be paired with another mode of analgesia, such as a nonsteroidal antiinflammatory drug, when used in rabbits.

SUMMARY

Tramadol may be an alternative to analgesics currently used in zoologic medicine. A few studies examining the effect of tramadol in zoologic species are available and they suggest that significant species differences exist in pharmacokinetics as well as analgesic dynamics. Until more research is available, recommended doses will be based solely on clinical experience. Clinicians at various zoologic institutions and exotic clinical practices are encouraged to perform clinical trials and aid in the determination of appropriate doses of tramadol for the many zoologic species present.

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